

REMARKS

Request for Continued Examination

A request for continued examination is filed along with this complete response to the Final Office Action mailed May 30, 2008.

Status of the Claims

Claims 1-34 are currently pending in the present application. By this paper, claims 1, 2, 4, 15, 16, 23, 24, 26, and 31 are amended. New claims 44-47 are introduced. Consideration of claims 1-34 and 44-47 is respectfully requested in view of the foregoing remarks and amendments presented.

Summary of Telephonic Interview

The Applicants thank Examiner Karpinski and Examiner Haghighatian for the courtesies extended during a telephone interview with Applicants' attorneys Charlton Shen and Christina Sperry on July 22, 2008. During the telephone interview, the indefiniteness rejections to claims 16, 24, and 26 were discussed. As well, claims 1 and 17 were discussed vis-à-vis cited U.S. Patent Nos. 6,050,990, 5,709,654. Though no agreement was reached regarding the claims, Applicants' attorneys believe that the present paper and remarks, along with the interview, should place the matter in disposition for allowance.

Amendments to the Claims

Independent claim 1 is amended to recite administering a pre-photosensitizing agent to *epithelial tissue and a targeted treatment site underlying the epithelial tissue*, preventing metabolism of the pre-photosensitizing agent in the *epithelial tissue*, while allowing the pre-photosensitizing agent to metabolize into a photosensitizing agent in tissue at the targeted treatment site, and irradiating the *targeted treatment site* to activate the photosensitizing agent at the targeted treatment site, wherein the epithelial tissue is substantially unaffected. Support for these amendments is found through the specification and drawings, such as in figure 1 and paragraph

[0029] of U.S. Patent Application Publication No. US 2004/0259855 A1, the published version of the present application (herein the “Published Application”).

Claims 2, 4, 15, and 23 are amended to utilize diction consistent with the amendment to claim 1.

Claim 31 is amended to correct a typographical error.

Claims 16, 24, and 26 are each amended to delete the clause “or greater than.” New dependent claims 44-46 recite deleted matter from, respectively, claims 16, 24, and 26.

New claim 47 depends from claim 2 and recites “maintaining at least a portion of the targeted treatment site at a temperature in a range between about 25°C and about 40°C.” Support for the recitation is found throughout the present application, for example at paragraph [0028] of the Published Application.

No new matter is added.

Applicants respectfully request entry of these amendments.

Definiteness

The Examiner rejects claims 16, 20, 22, and 24-26 pursuant to 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Applicant respectfully disagrees that claims 16, 20, 22, 24, and 26 are indefinite.

Claim 25

The Examiner did not specify any rejected language in claim 25. Claim 25 was previously amended in response to the Office Action dated November 15, 2007, which obviated the bases for the Examiner’s §112, second paragraph rejection presented in that Office Action. Applicant does not see any §112, second paragraph issues with pending claim 25 and respectfully requests the

Examiner to particularly point out the rejected language if claim 25 is again rejected pursuant to §112, second paragraph.

Claims 16, 24, and 26

Although Applicant does not agree with the Examiner that claims 16, 24, and 26 are indefinite, Applicant has amended claims 16, 24, and 26 to expedite prosecution, thereby obviating the Examiner's rejections. Applicant has also added new claims 43-46 as mentioned above.

Claims 20 and 22

Claims 20 and 22 stand rejected as being indefinite for the use of the term "substantially." The claims, however, are definite because the phrases "substantially destroy" and "substantially remove" in the context of the claims have a clear meaning to one skilled in the art. As discussed in Applicants previous paper, the use of the term "substantially" has been upheld in numerous court proceedings, as noted in MPEP §2173.05(b). Accordingly, its use *per se* is not prohibited.

Though the Final Office Action suggests that *substantially* is relative term which renders a claim indefinite, the Courts, as discussed in MPEP §2173.05(b), have clearly stated that "[t]he fact that claim language, including terms of degree, may not be precise, does not automatically render the claim indefinite under 35 U.S.C. §112, second paragraph. See *Seattle Box Co., v. Industrial Crating & Packing, Inc.*, 731 F.2d 818 (Fed. Cir. 1984). Furthermore, a claim term that is not defined in the specification is not indefinite if the meaning of the claim is discernable to one skilled in the art. See MPEP §2173.02 (citing *Bancorp Services, L.L.C. v. Hartford Life Ins. Co.*, 359 F.3d 1367, 1372 (Fed. Cir. 2004)).

Claim 20 recites that the step of irradiating the targeted treatment site with light is effective to *substantially destroy* the malignant cells. The use of photodynamic therapy (herein "PDT") to treat malignant cells is known to those skilled in the art, *see e.g.*, Fritsch et al., Photodynamic Therapy in Dermatology, Arch Dermatol, Vol 134, Feb 1998, pp. 207-214 (herein "Fritsch"), a copy of which is appended hereto. As noted in Fritsch, the use of PDT to treat diseases such as Basal Cell Carcinoma can lead to less than a 100% complete response rate (see *id.*, pg. 210, left hand column). Accordingly, a skilled artisan would readily understand the use of the phrase

“substantially destroy” in claim 20 given the variances inherent in the methods. Indeed, as the Federal Circuit has opined, the definiteness requirement of §112 second paragraph cannot be used to require more precision in language than the relevant technology permits or is capable of generating (see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986)). In a similar manner, claim 22’s recitation to substantially remove hair associated with the hair follicles is well understood by one skilled in the art since such a person is well versed in the aspects of hair removal by PDT, and the end result is well understood by a skilled artisan, *see e.g.*, Tankovich.

Accordingly, for at least these reasons, claims 20 and 22 are not indefinite.

Nonobviousness

The Examiner rejects claims 1-19 and 22 pursuant to 35 U.S.C. §103(a) as being obvious over U.S. Patent No. 6,050,990 (“Tankovich”) in view of U.S. Patent No. 5,709,654 (“Klatz”). Claims 20 and 21 stand rejected under 35 U.S.C. §103(a) as being obvious over Tankovich in view of Klatz as applied to claim 1, and in further view of U.S. Patent No. 5,955,490 to Kennedy et al. (herein “Kennedy”). Claim 23-34 stand rejected under 35 U.S.C. §103(a) as being obvious over Tankovich in view of Klatz as applied to claim 1, and in further view of U.S. Patent 5,114,973 to Hess et al. (herein “Hess”) and Kennedy. The claims, however, are all patentable at least because the combination of art neither teaches nor suggests the claimed invention to one skilled in the art.

Independent Claim 1

Amended claim 1 recites a method that includes administering a pre-photosensitizing agent to epithelial tissue and a targeted treatment site underlying the epithelial tissue and preventing metabolism of the pre-photosensitizing agent in the epithelial tissue, while allowing the pre-photosensitizing agent to metabolize into a photosensitizing agent in tissue at the targeted treatment site. The method also includes irradiating the targeted treatment site to activate the photosensitizing agent at the targeted treatment site, wherein the epithelial tissue at the treatment site is substantially unaffected.

As discussed in the present application (see paragraph [0004] of the Published Application), when a pre-photosensitizing agent is utilized in photodynamic therapy, the agent can be absorbed by

both the epidermal tissue and dermal tissue, where the latter can be the tissue targeted for treatment. As a result, application of light can cause phototoxicity to the epidermis, which can lead to long-lasting hyperpigmentation or epidermal necrosis (see *id.*).

Methods consistent with amended claim 1 potentially provide a solution to this problem. As disclosed in the present application through the description and examples therein, epithelial tissue can be protected when using PDT with a pre-photosensitizing agent by *preventing metabolism of the pre-photosensitizing agent in the epithelial tissue while allowing the pre-photosensitizing agent to metabolize into a photosensitizing agent in tissue at a targeted treatment site underlying the epithelial tissue* as recited in amended claim 1.

None of the art cited during the prosecution of the present application, alone or in combination, teaches, suggests, or hints of these recitations. Accordingly, the cited art does not render amended claim 1 obvious.

Tankovich provides no hint or suggestion of “*preventing metabolism of the pre-photosensitizing agent in the epithelial tissue while allowing the pre-photosensitizing agent to metabolize into a photosensitizing agent in tissue at the targeted treatment site*” where the “targeted treatment site underl[ies] the epithelial tissue.” As discussed in the Final Office Action, Tankovich discloses a sunlight-assisted hair removal technique in which a prodrug is absorbed by target hair growth cells through the skin. Subsequently, the skin is exposed to direct sunlight to activate the prodrug, thereby causing damage to the hair growth cells. See Tankovich, column 38, lines 45-57. The disclosure does not provide any hint of *preventing metabolism of the pre-photosensitizing agent in epithelial tissue while allowing the pre-photosensitizing agent to metabolize into a photosensitizing agent at the targeted treatment site*. In fact, this section of Tankovich does not even discuss metabolism of a pre-photosensitizing in any manner whatsoever; the reference actually contemplates direct sunlight activation of the photochemical applied to the skin. See *id.*, column 38, lines 51-54.

The Final Office Action also refers to a section of Tankovich which describes a technique for hair removal using a long pulse laser and skin cooling (see *id.*, column 63, line 15 through column 66, line 58). In this technique, an exogenous chromophore, such as carbon particles,

infiltrates hair ducts. A long pulse of light is used to heat the contaminant, which subsequently transfers its energy to the adjacent tissue (see *id.*, column 64, lines 32-36). The tissue undergoes a temperature increase to about 70°C to about 80°C (see *id.*, column 64, lines 4-5). Since such a high temperature is required to damage the hair cells, cooling at the skin surface is performed to avoid concurrent damage to other skin tissue due to overheating (see *id.*, column 63, lines 51-54). No pre-photosensitizing agent is discussed whatsoever. Accordingly, this disclosure of Tankovich also provides absolutely no hint or suggestion of *preventing metabolism of the pre-photosensitizing agent in epithelial tissue while allowing the pre-photosensitizing agent to metabolize into a photosensitizing agent at the targeted treatment site*. This discussion is also completely void regarding metabolism of a pre-photosensitizing agent.

The Final Office Action admits to so much of the lack of Tankovich's teachings with regard to claim 1.

Klatz does not remedy the deficiencies of Tankovich. Klatz is relied on to teach that cooling the body sufficiently will inhibit metabolism, and the production of free radicals, which cause tissue damage, will decrease. But there is no disclosure or hint of *preventing metabolism of a pre-photosensitizing agent in epithelial tissue while allowing the pre-photosensitizing agent to metabolize into a photosensitizing agent at a targeted treatment site*. Indeed, the sections of Klatz cited in the Final Office Action state:

Similar to the above-mentioned brain resuscitation solution, the organ preservation and resuscitation solution (hereinafter organ preservation solution), is chilled by cooling it to a sufficiently low temperature to inhibit **degenerative metabolism of the organ**. When the **organ's metabolism** is slowed, free radical production decreases (Klatz, column 4, lines 59-65, **emphasis added**).

and

At temperatures below normal body temperature, the **degenerative metabolism of the organ(s)** is slowed as the subsequent free radical production (O₂⁻ or other free radicals) decreases (Klatz, column 12, lines 62-65, **emphasis added**).

That is, Klatz is only directed to generalized techniques for inhibiting *degenerative metabolism of an entire organ* by utilizing techniques such as pumping a cold fluid through the organ. Such teachings are completely different from *preventing metabolism of a pre-photosensitizing agent in epithelial tissue while allowing the pre-photosensitizing agent to metabolize into a photosensitizing agent at a targeted treatment site*. Klatz does not contemplate pre-photosensitizing agents that are selectively metabolized in different parts of an organ, i.e., skin. As well, contrary to statements in the Final Office Action, Klatz does not teach the effect of temperature on the metabolism of a pre-photosensitizing agent such as aminolevulinic acid. Klatz only teaches inhibition of degenerative metabolism, such as associated with brain-death, by lowering free radical production. The method of amended claim 1, however, makes no mention of free radical reduction. In summary, Klatz in no way rectifies the teachings of Tankovich to render claim 1 obvious.

The Final Office Action states that

“Although Tankovich et al. does not teach cooling a treatment area to prevent metabolism of a protoporphyrin precursor to a protoporphyrin it would have been obvious to a skilled artisan that to combine methods of photodynamic therapy which embrace using aminolevulinic acid with the knowledge that cooling the body slows down the process of metabolism. It was well known at the time of the invention that the body naturally metabolizes aminolevulinic acid into a protoporphyrin, and that metabolism is slowed down with lower temperatures. It was also well known at the time of the invention that irradiation of a protoporphyrin causes tissue damage but that irradiation of aminolevulinic acid does not cause tissue damage. A skilled artisan would have recognized that it would be possible to prevent unwanted tissue damage by simply cooling the area surrounding the treatment site to prevent the metabolism of aminolevulinic acid into a photosensitive compound before irradiating the area intended for treatment” (underline added).

Even assuming *arguendo* the underlined assumptions of the above cited paragraph, a skilled artisan would still not arrive at amended claim 1, or claims 2 or 4 in light of the direct discussion regarding cooling. At best, a skilled artisan may have recognized that irradiating skin infiltrated with aminolevulinic acid (herein “ALA”), where the skin was precooled before irradiation, could inhibit tissue damage vis-à-vis not precooling the skin. This, however, is not amended claim 1. The claimed invention recites *preventing metabolism of a pre-photosensitizing agent in the epithelial*

tissue while allowing the pre-photosensitizing agent to metabolize into a photosensitizing agent at the targeted treatment site, where the targeted treatment site underlies the epithelial tissue.

Indeed, it is only with the disclosure of the present application that the Final Office Action can conclude that amended claim 1 is obvious, i.e., through the use of impermissible hindsight. Though the Final Office Action suggests hindsight reasoning is permissible, it also states that the reasoning is only proper if it “does not include knowledge gleaned only from the application’s disclosure.” The cited art, however, provides no recognition whatsoever that a pre-photosensitizing agent can be prevented from metabolizing in epithelial tissue while the pre-photosensitizing agent in the underlying targeted tissue site is metabolized. That teaching is only gleaned through the present application. Accordingly, the Final Office Action’s reconstruction of claim 1 is improper.

While Applicants maintain their arguments in previously submitted papers regarding the lack of reason/motivation to combine the cited art or to combine the teachings of the disparate techniques discussed in Tankovich, such arguments are not necessary because the combined art simply lacks the ability to teach or suggest the recitations of the claimed invention.

Accordingly, for at least these reasons, amended claim 1 is patentable over Tankovich and Klatz.

Dependent Claims 2-19 and 22

Claims 2-19 and 22 each depend ultimately from amended claim 1. Accordingly, each is patentable over the cited art at least for the same reasons that amended claim 1 is patentable. However, the dependent claims are also patentable for other independent reasons.

For example, claim 16 recites that tissue *at the targeted treatment site* is heated to a temperature that is equal to about 25° C. Claim 17 recites that tissue *at the targeted treatment site* is heated to a temperature in the range of about 25° C to 40° C. The Examiner cites column 3, lines 40-54 of Tankovich as disclosing such a feature, but neither this portion nor any other portion of Tankovich discloses the claimed heating of tissue.

Tankovich at column 3, lines 40-54 discloses that the *skin surface* one to two hair follicle radii from the hair duct wall is heated to no more than 10° C above body temperature, but that is not the *targeted treatment site*. The targeted treatment site is at the site of the hair follicle desired to be damaged, surrounding the base of the hair duct, which Tankovich discloses is heated to about 70° C to 80° C. Col. 63, line 59 to col. 64, line 9; col. 64, lines 38-44; col. 65, lines 1-14; Fig. 32. Tissue at the targeted treatment site in Tankovich is thus clearly not at a temperature that is equal to about 25° C, as recited in claim 16, and is clearly heated above the temperature range recited in claim 17.

Dependent Claims 20 and 21

At least for the reasons discussed above, Tankovich and Klatz do not make obvious independent claim 1. Kennedy is relied on only for dependent claim features, namely that the targeted treatment site can include malignant cells or sebaceous glands, and does not remedy the deficiencies of Tankovich and Klatz. Accordingly, claim 20-21 distinguish over Tankovich, Klatz, and Kennedy, either taken alone or together, and are allowable at least because they depend from an allowable base claim.

Dependent Claims 23-34

At least for the reasons discussed above, Tankovich, Klatz, and Kennedy do not make obvious independent claim 1. Hess is relied on only for dependent claim features, namely that succinylacetone is an inhibitor of ALA, and does not remedy the deficiencies of Tankovich, Klatz, and Kennedy. Accordingly, claim 23-34 distinguish over Tankovich, Klatz, Kennedy, and Hess either taken alone or together, and are allowable at least because they depend from an allowable base claim. The claims, however, are also allowable for other independent reasons.

For example, claim 23 recites that the step preventing metabolism of the pre-photosensitizing agent in epithelial tissue comprises applying a chemical inhibitor to the epithelial tissue. The Final Office Action concedes that neither Tankovich nor Klatz discloses applying a chemical inhibitor to prevent metabolism of the pre-photosensitizing agent. Kennedy is only relied on by the Examiner for a particular concentration of ALA. The Final Office Action then asserts that Hess teaches that succinylacetone is an inhibitor of ALA, and concludes that claim 23 is obvious.

But Hess, like Tankovich and Klatz, does not teach the recitation of claim 23. Assuming *arguendo* the Final Office Action's statement, Hess *only* teaches that succinylacetone is an inhibitor of ALA. The reference is void of any teaching, suggestion, or hint of applying a chemical inhibitor to epithelial tissue to prevent metabolism of a pre-photosensitizing agent as part of a method for protecting epithelial tissue during photodynamic therapy. Accordingly, the combined art does not even teach the recitations of claim 23.

A prima facie case of obviousness cannot be established by merely pointing out the existence of particular claim elements in the prior art. MPEP §2143 and the Supreme Court's recent decision in *KSR Int'l Corp. v. Teleflex, Inc.*, 127 S. Ct. 1727 (2007) underscore the deficiencies in the Office Action and the error of its obviousness rejection of claim 23. The Supreme Court said that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 127 S. Ct. at 1741. The Examiner states that it would be obvious to combine the teachings of Tankovich, Klatz, Hess, and Kennedy "in order to prevent damage to tissue surrounding a site being treated with photodynamic therapy" but does not provide any analysis why that is true.

To make a prima facie showing of obviousness of a claimed invention, the Examiner should "identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *Id.*; see MPEP §2141, §2143.01(IV). Where no such explanation is given, as is the case here, improper use of hindsight can be inferred. Here, the Office Action makes conclusory statements suggesting use of the succinylacetone disclosed in Hess with the hair removal scheme of Tankovich in view of Klatz with no reason to do so aside from preventing damage to selected tissue, which is nonsensical given that Tankovich teaches irradiating *all* tissue exposed to ALA to inhibit hair growth.

The fact that succinylacetone exists in the prior art does not bar patentability. It is only with the benefit of Applicant's disclosure that the Examiner is able to point to a chemical disclosed in another reference and suggest combining it with Tankovich and Klatz. That the Examiner, after

having read Applicant's disclosure, can look at Tankovich and Klatz, which the Examiner admits does not disclose application of a chemical inhibitor, and choose to use the succinylacetone of Hess with Tankovich and Klatz does not bar patentability. Tankovich's Method No. 8 involves exposing all ALA-covered skin to sunlight, and there is no reason or motivation to use a chemical inhibitor with the ALA absent hindsight using Applicant's application as a road map. Thus, it would not have been obvious at the time of the invention to combine Hess with Tankovich, Klatz, and Kennedy, so claim 23, and hence also claims 24-34 which depend therefrom, represent allowable subject matter.

Accordingly, claim 23 is not obvious over the cited combination. Claims 24-34 each depend ultimately from claim 23. Thus, each is also patentable for at least the same reasons given for claim 23.

New Claims 44-47

New claims 44-47 each depend ultimately from claim 1. Accordingly, each is patentable for at least the same reasons that claim 1 is patentable. Moreover, claims 45 and 46 each depend from claim 23. Accordingly, each is also patentable for the reasons given for claim 23. Claim 47 is similar to claim 17, though dependent on a different base claim. Accordingly, it is also patentable for the reasons given above for claim 17.

CONCLUSION

Applicant submits that all pending claims are in condition for allowance, and allowance thereof is respectfully requested. Applicant's amendment of the claims does not constitute a concession that the claims are not allowable in their unamended form. The Examiner is encouraged to telephone the undersigned attorney for Applicant if such communication is deemed to expedite prosecution of this application.

In the event that a petition for an extension of time is required to be submitted at this time, Applicant hereby petitions under 37 CFR 1.136(a) for an extension of time for as many months as are required to ensure that the above-identified application does not become abandoned.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 141449, under Order No. 22727-110.

Dated: *2 September 2008*

Respectfully submitted,

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